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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/817,538	03/26/2001	Zuomei Li	106101.144	6847

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EXAMINER	
LACOURCIERE, KAREN A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/817,538	LI ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5 and 7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

In view of the Appeal Brief filed on 04-19-2004 and a new sequence search, PROSECUTION IS HEREBY REOPENED. A new ground of rejection is set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Terminal Disclaimer

The terminal disclaimer filed on 09-15-03 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of 09/817,913 has been reviewed and is accepted. The terminal disclaimer has been recorded.

New Grounds of Rejection

Claim Rejections - 35 USC § 102 or 35 USC § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 102(b) or 35 USC 103(a) as being anticipated by or obvious over Accession Number AA469268 from NCI-CGAP (National Cancer Institute, Cancer Genome Anatomy Project).

NCI-CGAP discloses a 25-mer oligonucleotide that is fully complementary to residues 19-46 of SEQ ID NO:2 HDAC-1. The oligonucleotide disclosed by NCI-CGAP meets all of the structural requirements of the instant claims, being fully complementary to SEQ ID NO:2 and falling within the length range of 15 to 26 nucleotides.

Since the prior art oligonucleotides meet all the structural limitations of the claims, the prior art oligonucleotides would then be considered to "inhibit expression" of

histone deacetylase forms, as claimed, absent evidence to the contrary. See, for example, MPEP § 2112, which states "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. 'There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102.' In re Best, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims."

Therefore, the instant invention is anticipated or obvious over Accession Number AA469268 from NCI-CGAP.

Claim Rejections - 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al. (IDS reference A3, IDS filed 10/09/01) in view of the collection of Taylor et al. (*DDT* Vol. 4, No. 12, 12/12/99, pages 562-567), Bennett et al. (Chapter 2,

pages 13-46, from Methods in Molecular Medicine: Antisense Therapeutics, 1996), Baracchini et al. (U.S. Patent 5,801,154) and Cowsert (U.S. Patent 5,951,455) and the sequence of HDAC01 (instant SEQ ID NO:2 from GenBank Accession No. U50079, Applicants own admission, page 9 of specification) for the same reasons of record set forth in the Official actions.

Yoshida et al. is relied upon to teach motivation to specifically inhibit a histone deacetylase for the study of the role of histone acetylation in controlling the chromatin functions in eukaryotic cells (page 17174). They teach that a long felt need existed in the art for "the use of a more specific and potent inhibitor of histone deacetylase... to carry out further more refined analyses" of the role of histone deacetylase. While they taught use of TSA as "an important tool in the analysis of the role of histone acetylation in the regulation of the chromatin structure, differentiation, and the cell cycle" they did not specifically teach antisense to histone deacetylase as a research tool for gene inhibition.

Taylor et al. are relied upon to teach generation of antisense oligonucleotides as a tool in the "efficient evaluation of the sequence data generated by the Human Genome Project" (abstract). They define antisense oligonucleotides as: "short sequences (7-30 nucleotides) of nucleic acids that bind to a specific region of a target messenger RNA (mRNA)... and can be designed to inhibit any gene target provided that the sequence is known. The specificity and ease of design of ONS make them attractive candidates as therapeutic agents and as research tools for the elucidation of gene function." They further teach on page 563 the rational for modifications of the

antisense oligonucleotide including "the incorporation of alkyl groups at the 2'-O position of ribose" to increase the binding affinity of ONS for their target. They teach that not all of the 2'-O positions should be modified since that prevents RNAse H degradation of the oligonucleotide target complex. They do not specifically teach antisense to HDAC-1.

Bennett et al. are relied upon to teach that "the antisense paradigm offers the opportunity to identify rapidly lead compounds based on knowledge of the biology of a disease process, and a relevant target gene sequence. With this information, the practitioner of antisense drug discovery can rapidly design, synthesize, and test a series of compounds in cell culture and determine if the target gene is specifically inhibited." (Page 13) They provide the overall process for design and use of antisense oligonucleotides based on the knowledge of a target gene sequence, but do not provide specific motivation for design of antisense to HDAC-1.

GenBank Accession No. U50079 taught that the sequence of human HDAC-1 (instant SEQ ID NO:2) was known.

Baracchini et al. and Cowsert et al. are both relied upon to teach design of antisense oligonucleotides to a known gene target and modifications of said antisense for improved function *in vitro*. Specifically, Baracchini et al. teach in cols. 4-10 the motivation to design antisense to a known gene target and methods for modifying said antisense for increased expression. Cowsert et al. teach in cols. 3-12 and 25-32 teach the motivation to design antisense to a known gene target and methods for modifying said antisense for increased expression. Cowsert specifically teaches design of an antisense having 8 to 30 bases (see claim 1). They teach the claimed modifications

(hybrids and chimeras as defined on pages 19-20 of the instant specification) of antisense as follows: modified internucleoside linkage; phosphorothioate linkage; at least one modified sugar moiety; a 2'-O-methoxyethyl sugar moiety; at least one modified nucleobase; a 5-methylcytosine base (Cowsert col. 25-col. 34). They also teach a chimeric oligonucleotide (Cowsert col. 33). They taught by example addition of 2'-O-methyl modifications on the wings (5' and 3' ends) of the disclosed antisense oligonucleotides. They do not specifically teach design of antisense to the HDAC-1 gene as instantly claimed.

It would have been *prima facie* obvious to one of ordinary skill in the art to design an antisense to any gene target specifically as a tool for the investigation of the expressed protein function (Taylor et al.), or for the identification of drug candidates (Bennett et al.). It would have been *prima facie* obvious to one of ordinary skill in the art to design an inhibitor of a histone deacetylase, including the instant HDAC-1, for the reasons taught by Yoshida et al. It would have been *prima facie* obvious for one of ordinary skill in the art to have considered the teachings of Taylor et al., Bennett et al., Cowsert and Baracchini et al. for a design of an antisense oligonucleotide having about 13 to about 35 or about 15 to about 26 nucleotides in length, or having 20-26 nucleotides in length and having 2'-O-methyl modifications, specifically targeting the HDAC-1 gene of instant SEQ ID NO:2, since (1) the sequence of human HDAC-1 was known in the art in Genbank Accession U50079 from which to design the complementary antisense sequences, and (3) these claimed sizes and modifications were all disclosed by Taylor et al., Bennett et al., Cowsert and Baracchini et al. as

routinely used in the art for improved antisense stability. It thus would have been obvious to one of ordinary skill in the art at the time that the invention to design of oligonucleotides such as those instantly claimed to bind HDAC-1 as a tool for gene specific inhibition of HDAC-1.

One of ordinary skill in the art would have been motivated to make specific inhibitors to histone deacetylase for the reasons taught by Yoshida et al., analysis of the role of the histone deacetylase in the regulation of chromatin structure, differentiation and the cell cycle. One would have been motivated to use antisense as a tool for inhibition of any gene target such as HDAC-1 for the reasons taught by Taylor et al., Bennett et al., Cowsert and Baracchini et al. above. One of ordinary skill in the art thus would have been motivated to combine the teachings of Yoshiba et al. with the teachings of Taylor et al., Bennett et al., Cowsert and Baracchini et al. for making oligonucleotides to inhibit HDAC-1 as instantly claimed as the mechanism for HDAC-1 gene inhibition.

One of ordinary skill in the art would have had an expectation of success to design antisense sequences to HDAC-1 since Bennett et al., Taylor et al., Cowsert and Baracchini et al. all taught that the design of an antisense requires no more than knowledge of the target gene nucleic acid code sequence from which to design the complementary oligos (optionally complexed with modifications thereof for improved inhibition of the target gene in cells in culture) and the sequence of HDAC-1 was known in the art at the time the invention was made.

Response to Arguments

Applicant's arguments filed 04-19-2004 have been fully considered but they are not persuasive. In response to the rejection of record of claims 1-3 and 5 as over Yoshida et al. (IDS reference A3, IDS filed 10/09/01) in view of the collection of Taylor et al. (*DDT* Vol. 4, No. 12, 12/12/99, pages 562-567), Bennett et al. (Chapter 2, pages 13-46, from Methods in Molecular Medicine: Antisense Therapeutics, 1996), Baracchini et al. (U.S. Patent 5,801,154) and Cowsert (U.S. Patent 5,951,455) and the sequence of HDAC01 (instant SEQ ID NO:2 from GenBank Accession No. U50079, Applicants own admission, page 9 of specification) Applicant argues there is no motivation or suggestion in the references cited or in the knowledge generally available in the prior art to combine the teachings of the cited references. Applicant argues that the primary reference Yoshida et al. sets forth a technical problem to find a more potent and specific inhibitor of HDAC-1 than n-butyrate and that Yoshida et al. solve this problem by finding another small molecule inhibitor, TSA. Applicant argues that TSA is the more potent and specific inhibitor Yoshida describes a need for and there is no mention explicitly or implicitly within Yoshida to search outside of the small molecule art for other HDAC-1 inhibitors. Applicant argues that the need to combine five references emphasizes their arguments.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the

references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the general knowledge of the art indicates that antisense provides a means to specifically inhibit the expression of a target gene for the types of studies proposed by Yoshida et al., this art recognized knowledge is exemplified by the teachings of Taylor et al. and Bennett et al., for example.

Yoshida et al. clearly teach that there is a need to find a more potent and specific inhibitor of histone deacetylase for analysis of histone deacetylase activities. Yoshida et al. further discuss how the only other known histone deacetylase inhibitor, n-butyrate, has additional, multiple non-specific effects on cells. Yoshida et al. indicate that TSA appears to be a more specific inhibitor with fewer side effects than n-butyrate and therefore a useful tool for determining histone deacetylase activites in cells. The skilled artisan would clearly recognize the need to have other specific inhibitors of histone deacetylase as tools in elucidating the function of histone deacetylase, for example, to determine what TSA effects are, in fact, specific for histone deacetylase function, rather than non-specific TSA effects. Activity analysis for histone deacetylase, as taught and motivated by Yoshida et al., clearly would require multiple inhbitors as research tools. Yoshida et al. do not suggest that TSA is the only specific inhibitor needed for this analysis, and further, Yoshida et al. point to the shortcomings of the only other known inhibitor and teach comparative analysis using both inhibitors to elucidate specific versus non-specific effects. The skilled artisan would clearly recognize that other

comparative experiments using other specific inhibitors would be useful and that antisense would fulfill that need, based on the teachings of the secondary references and would further recognize the advantages of the improved specificity provided by antisense over the small molecule inhibitors known in the art for HDAC-1. Antisense was a commonly known and art accepted method of inhibition of a target gene in cells in cell culture and thus would have been an obvious choice for making a specific inhibitor of HDAC-1.

In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

Conclusion

Claim 7 is considered free of the prior art since the prior art did not teach nor fairly suggest the sequences of instant SEQ ID NOS: 17 and 18.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (571) 272-0759. The examiner can normally be reached on Monday-Thursday 7:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone

number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Lacourciere
July 7, 2004

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PRIMARY EXAMINER

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